REMARKS

Claims 50, 52 to 55 , 58, 59, 66 and 67 are currently pending. Claims 66 and 67 have been added. Support for the new claims can be found throughout the specification, e.g., at page 15, col. 1, paragraph [0135] of U.S. Publication No. 2002/0013275. No new matter has been added.

Status of Claims and Interview Summary

Applicants acknowledge with thanks Examiner Vivlemore's Interview Summary dated March 17, 2010. In particular, applicants note with appreciation the Examiner's recommendation that a new claim set be submitted in the present Reply that reflects the fact that claim 55 remains pending in this case. Applicants apologize for any inconvenience caused by their inadvertent omission of claim 55 in their previously-submitted claim set.

Withdrawn Rejections

Although not explicitly mentioned in the present Office Action, applicants acknowledge the Office's withdrawal of the previous rejection of claims 50, 52 to 55, and 59, under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 103

Claims 50, 52 to 55, and 58 to 59 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 5,171,217 ("March") in view of U.S. Patent No. 5,413,797 ("Khan"), U.S. Patent No. 4,919,939 ("Baker"), U.S. Patent No. 4,233,968 ("Shaw"), and U.S. Patent No. 4,942,184 ("Haugwitz"). Applicants again respectfully traverse for the reasons discussed below.

March, the Office's primary reference, discloses delivering a drug carried by a biodegradable polymer microparticle to an affected intramural site for sustained release in conjunction with or following balloon catheter procedures. March's biodegradable microparticles are injected under direct pressure into the wall of a body vessel in the region of the affected site. (See, e.g., March, Abstract). Applicants' claims, on the other hand, recite, e.g., a method that includes locally administering to a human a biocompatible, non-biodegradable

sustained release dosage form including a cytostatic amount of a therapeutic agent dispersed in a polymer matrix for reducing restenosis following a vascular surgical procedure. The cytostatic amount of the therapeutic agent inhibits a vascular smooth muscle cell activity without killing the cell. The deficiencies of March as the primary reference are therefore considerable. March fails to disclose using non-biodegradable polymers, which is a deficiency that is acknowledged by the Office (see the Office Action at page 3). Further, March discloses a long list of classes of smooth-muscle cell inhibitors that might conceivably be included in their biodegradable microcarrier (see, e.g., March, col. 3, line 34 – col. 4, line 8), but fails to disclose or suggest applicants' specifically-recited therapeutic agents. Further still, March fails to teach or suggest administering a cytostatic amount of a therapeutic agent that inhibits a vascular smooth muscle cell activity without killing the cell, as applicants claim.

In their previous Reply, applicants first pointed out the deficiencies of March and explained why none of Khan, Baker, Shaw, or Haugwitz, individually or in combination, cures those deficiencies. In the present Office Action, the Office responds by, *inter alia*, pointing to applicants' statement that a skilled practitioner would not have looked to Khan, Baker, Shaw, and Haugwitz to satisfy March's deficiencies because they are wholly unrelated to methods of reducing restenosis, and states that these reference were not cited to teach reduction of restenosis, but as evidence that skilled practitioners recognized that both biodegradable and non-biodegradable polymers were routinely used in sustained-release compositions (see Office Action at page 5).

Accordingly, applicants understand the Office's position to be that skilled practitioners would have replaced March's biodegradable microparticles with non-biodegradable microparticles in an attempt to arrive at the present invention. Applicants respectfully disagree and submit that the Office's proposed modification would require one to ignore or reject important teachings of March. A skilled practitioner, reading March, would note how critical March asserts biodegradability of the microparticles is to the described method. For example, at col. 2, lines 58 to 62, March states (emphasis added):

> The drugs are released slowly, providing a residence time sufficient for treatment or control at the site of smooth muscle cell proliferation in the case of restenosis following angioplasty. The polymeric material degrades and *diffuses inoffensively*.

Further, at col. 6, lines 32 to 35, March further explains, at least in part, why the biodegradability of the microparticle to be injected into a vessel wall is essential to March's method, stating (emphasis added):

> *The microparticles are biodegradable*. Their use therefore avoids the necessity of leaving foreign substances in the body for an extended period with attendant possible complications.

Given such statements, one can see that March viewed biodegradability as integral to the March method. However, under the Office's proposed combination of March, Khan, Baker, Shaw, and Haugwitz, one would have to ignore or flatly reject these teachings. This combination of references is therefore improper at least because a skilled practitioner, reading March and understanding the benefits of the process as described by this reference, would have been led away from using non-biodegradable polymers. Further, the Office's proposed modification would change the principle of operation of the March method, which renders this combination of references insufficient to establish a *prima facie* case of obviousness. The impropriety of combining references in such a way is set forth in the MPEP at §21430.02, which states:

> [i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious.

Further, applicants reiterate that no skilled practitioner, reading March, Khan, Baker, Shaw, and Haugwitz, would have combined their teachings in an attempt to arrive at a method that includes using the specifically-recited therapeutic agents, and in amounts that inhibit a vascular smooth muscle cell activity without killing the cell. None of March, Khan, Baker, Shaw, or Haugwitz, discloses or suggests this subject matter. March discloses many classes of smooth-muscle cell inhibitors that might conceivably be included in a biodegradable microparticle, but fails to disclose or suggest applicants' specifically-recited therapeutic agents and the local administration of a cytostatic amount of those agents to inhibit a vascular smooth muscle cell activity without killing the cell. No skilled practitioner would have looked to Khan,

Baker, Shaw, or Haugwitz to remedy these deficiencies. As discussed previously, these references are directed to adrenocorticotropic hormone compositions, compositions for oral indications, intrauterine devices, and taxol compositions useful for their highly cytotoxic properties. The Office cites Haugwitz generally for disclosing taxol, but upon reading Haugwitz, a skilled practitioner would have had no reason to believe that taxol could even be used in a cytostatic manner, as applicants claim. None of these secondary references provides the information missing from March and no skilled practitioner would have been led to combine them with March in an attempt to arrive at the claimed invention.

Moreover, even if a skilled practitioner were to combine the teachings of March, Khan, Baker, Shaw, and Haugwitz, applicants' methods still would not have been obtained. This is because, *inter alia*, the resulting method would not require locally administering a TGF-beta production or activation stimulator, TGF-beta, tamoxifen, a nuclear enzyme DNA topoisomerase II inhibitor, a DNA polymerase inhibitor, an RNA polymerase inhibitor, an adenyl guanyl cyclase inhibitor, a superoxide dismutase inhibitor, a terminal deoxynucleotidyl-transferase, a reverse transcriptase, lovastatin, vinblastin, cytochalasins, taxol, taxotere, trichothecene, *Pseudomonas exotoxin*, a chemotactic factor inhibitor, a chemotactic factor receptor inhibitor, an intracellular cytoskeletal protein inhibitor, a caffeic acid derivative, nilvadipine, a steroid hormone, sphingosine, somatostatin, or N-ethylmaleimide, or administering such agents in a cytostatic amount that inhibits a vascular smooth muscle cell activity without killing the cell.

March, Khan, Baker, Shaw, and Haugwitz, alone and in combination, fail to teach or suggest the subject matter recited in applicants' claims. No skilled practitioner would have found any motivation to combine these references, nor would they have arrived at the present invention even if they had done so. Thus, applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness against the presently claimed methods. Accordingly, applicants respectfully request that the rejection of claims 50, 52 to 55, and 58 to 59 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Finally, new claims 66 and 67 are not obvious in view of this combination of references. New claim 66 recites a method wherein local administration includes administering the biocompatible, non-biodegradable sustained release dosage form intraluminally. Claim 67 recites a method wherein locally administering includes delivering a cytostatic amount of the

biocompatible, non-biodegradable sustained release dosage form to the proximal 6 to 9 cell layers of the tunica media smooth muscle cells lining the lumen of a vessel. March, on the other hand, describes a method wherein March's biodegradable microparticles are injected under directed pressure into the wall of a vessel. March's description makes clear that injection, rather than, e.g., intraluminal administration, is integral to the method. For example, with respect to the choice of catheters for implementing March's method, March states (at col. 6, lines 9 to 19):

> Suitable catheters are those designed to provide a chamber to minimize downstream escape of microparticles under the pressures required for arterial (or other organ) wall penetration. Conventional catheters can be modified for lateral discharge into the arterial wall. U.S. Pat. Nos. 4,824,436 (Wolinsky), 4,423,725 (Baran et al.) and 3,173,418 (Baran et al.) illustrate catheters suitable for use with this invention. Whatever specific design is chosen, pressures in the range of about 2 to about 10 atm. assure adequate penetration consistent with containing the discharge against undue downstream escape.

Futher, March explains at least in part why injection, as opposed to, e.g., intraluminal administration, is important to March's method, stating (at col. 6, lines 27 to 31; emphasis added)

> *Since the microparticles are not in direct contact with the blood*, the likelihood of thrombosis is greatly reduced. Because the microparticles are of minute size, distal embolization is unlikely to cause serious restriction of bloodflow in the affected artery.

Accordingly, it is clear that March does not disclose, or even suggest, a method wherein local administration includes administering a biocompatible, non-biodegradable sustained release dosage form intraluminally or a method wherein locally administering includes delivering a cytostatic amount of a biocompatible, non-biodegradable sustained release dosage form to only the proximal 6 to 9 cell layers of the tunica media smooth muscle cells lining the lumen of a vessel. Khan, Baker, Shaw, and Haugwitz would not remedy such deficiencies. Accordingly, applicants also submit that claims 66 and 67 are not obvious in view of this combination of references.

CONCLUSION

Applicants believe that all of the pending objections/rejections have been addressed and that the claims are in condition for allowance. However, the absence of a reply to a specific rejection, issue, or comment does not signify agreement with or concession of that rejection, issue, or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper, and the amendment or cancellation of any claim does not signify concession of unpatentability of the claim prior to its amendment or cancellation.

Applicants request that the $490 charge for the Petition for Extension of Time fee for a two-month extension, and any other required fees, be charged to applicants' deposit account 06-1050, referencing Attorney Docket No. 10527-1108006.

Respectfully submitted,

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